

Remarks

Claims 1-22 are pending in the instant application. Claims 1-22 stand rejected under 35 U.S.C. §112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Claims 21 and 22 stand rejected under 35 U.S.C. §101 as improperly defining a process. Claims 1-12 and 15-22 stand rejected under 35 U.S.C. §102(b) as being anticipated by Apfel (WO 97/25097). Claims 1-12 and 18-22 stand rejected under 35 U.S.C. §102(b) as being anticipated by either Berg (WO 94/21301) or Lohrmann (United States Patent No. 5,716,597). Claims 1-22 stand rejected under 35 U.S.C. §103(a) as being anticipated by any one of Apfel, Berg, or Lohrmann in view of Unger (WO 98/10799). Claims 21 and 22 have been cancelled, without prejudice. The rejections are respectfully traversed. Reconsideration is respectfully requested.

Claim rejections – 35 USC §112:

Claims 1-22 stand rejected under 35 U.S.C. §112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. This rejection is respectfully traversed.

The Examiner objects to claim 1 reciting “heterogeneous gas-containing nucleation sites”. The Examiner considers the term “heterogeneous gas-containing nucleation sites” to be indefinite for failing to particularly point out and distinctly claim the subject matter. Applicants respectfully disagree with this characterization of the term. In the field of controlled particle, droplet and bubble formation the terms “heterogeneous nucleation” and “homogeneous nucleation” are well established and well recognised terms. Evidence that these terms were well known to the person skilled in the art at the priority date of the present application (22 April 1998) is provided by the following book extract (copy enclosed):

"Controlled Particle, Droplet and Bubble Formation", David J. Wedlock (Editor), Butterworth-Heinemann (1994), Section 6.2, pages 161-177.

The Examiner's attention is directed to p161 where the statement is made:

"Bubbles may arise spontaneously from six quite separate and essentially independent sources, and in each case after their formation, growth to a microscopic size may take place:

- (a) homogeneous nucleation,
- (b) heterogeneous nucleation ..."

Applicants stress that these modes are described as "quite separate and essentially independent". The terms are more fully defined in the subsequent text. Thus, the second paragraph on p. 162 states:

"When bubbles are formed in the bulk of the liquid, well away from any surface (for example, the walls of the container, dust particles or other foreign bodies, or the free liquid surface), the nucleation is said to be 'homogeneous'."

On page 167:

"Bubbles formed at a surface (e.g. the walls of the container, specks of dust or other inhomogeneities), rather than in the bulk of the solution, are said to be nucleated 'heterogeneously'."

Applicants contend that the terms 'homogeneous nucleation' and 'heterogeneous nucleation' are therefore well established, defined terms in the field of bubble formation. The enclosed reference further emphasises this fact *via* the statement at p.163:

"The theory of both homogeneous and heterogeneous nucleation has been covered extensively in the literature. Particularly comprehensive reviews have been given by Hirth and Pound (1963), and by Zettlemoyer (1969), while an earlier work by Dunning (1955) is still unsurpassed for clarity".

This shows that these terms have been used extensively in the field, and their definition has been known for many decades.

A nucleation site is the place on the surface where the bubble nucleation takes place. Nucleation sites can be added deliberately to a system to enhance bubble formation. The most natural way is to add small particles since these will have a large surface area. In that case, the whole particle may be called a nucleation site.

The Examiner refers to the term "gas-containing heterogeneous nucleation sites". Applicants stress that the present invention provides oil-in-water emulsion ultrasound contrast agents having separate (i.e. heterogeneous) nucleation sites associated with the emulsion droplets. Thus, the ultrasound contrast agents of the present invention are oil-in-water emulsions which have been modified in such a way that gas-containing nucleation sites are associated with droplets of the dispersed oil phase. An illustration of this would be when the surface of the added particle further comprises a gas, e.g. in a pore or by other means encapsulated into the surface. The present invention teaches that heterogeneous nucleation may be further promoted at that particular nucleation site.

The specification describes various methods in which these gas-containing nucleation sites can be provided - see: Page 8 line 29 to page 9 line 31; Page 11 line 13 to page 12 line 13; Example 2 and comparative Example 3; and Example 5 and comparative Example 6.

In view of the above, Applicants respectfully submit that the use of the term "heterogeneous gas-containing nucleation sites" in Claim 1 is clear to the person skilled in the art. Additionally, the Examiner's comments with respect to claims 21 and 22 are obviated by the cancellation of those claims. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim rejections 35 USC § 101:

Claims 21 and 22 stand rejected under 35 U.S.C. §101 as improperly defining a process. Applicants respectfully submit that this rejection is obviated by the cancellation, without prejudice, of claims 21 and 22. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim Rejections – 35 USC § 102:

Claims 1-12 and 15-22 stand rejected under 35 U.S.C. §102(b) as being anticipated by Apfel (WO 97/25097). The rejection is respectfully traversed.

Applicants submit that the oil-in-water dispersions of WO 97/25097 (hereinafter, the '097 reference) are simply that, i.e. no further materials which could provide nucleation sites, in particular gas-containing nucleation sites, are added. Hence, the dispersions of '097 neither contain nor comprise heterogeneous nucleation sites. As is described in the present application, in order to provide the heterogeneous nucleation sites, it is necessary to add an additional component. Preferred examples of these are claimed and recited in Claim 3. In Example 4b, hollow (i.e. gas-containing) polymer-stabilised nanocapsules from step (a) are added to a mixture of perfluorodimethylcyclobutane and perfluoroctanoic acid, followed by shaking. As described at page 18 lines 11 to 14, this gives a dispersion of gas-filled nanocapsules dispersed in a perfluorocarbon. This fluorocarbon dispersion is then shaken with water (lines 14 to 16) to give the desired fluorocarbon emulsion containing gas-filled nanocapsules within the fluorocarbon droplets. The emulsion thus contains fluorocarbon droplets and within the droplets are the gas-filled nanocapsules.

In contrast, '097 teaches emulsions of “drop material” in an aqueous liquid (see page 12 lines 6-19 of '097). There is no teaching or suggestion in this document of the use of additional materials providing gas-containing nucleation sites.

Applicants also point out that '097 does envisage that the vaporisation process for the emulsions therein will be homogenous nucleation, not heterogeneous, - please see page 7 lines 2 to 9; and page 13 lines 2 to 13, of '097.

Applicants stress that heterogeneous and homogeneous nucleation are known to be "quite separate and essentially independent" (see reference cited above), and hence use of this language in claim 1 confers novelty over prior art disclosing only homogeneous nucleation. Also, as discussed above applicants contend that ultrasound contrast agents comprising injectable oil-in-water emulsions wherein there are heterogeneous gas-containing nucleation sites are not taught or suggested in '097. Consequently, Applicants respectfully submit this document fails to disclose, teach, or suggest the elements of claim 1. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1-12 and 18-22 stand rejected under 35 U.S.C. §102(b) as being anticipated by either Berg (WO 94/21301). The rejection is respectfully traversed.

WO 94/21301 discloses solid microparticles which may act as nucleation sites. There is no suggestion that such microparticle should be gas-containing. In contrast, the present invention claims gas-containing microparticles. Where solid microparticulate nucleation sites are used in accordance with the present invention, these are chosen to have properties such as porosity or surface irregularities such that they contain gas. This is described at page 8 line 37 to page 9 line 9 of the present specification (especially p.9 lines 4 to 7). Nowhere does Berg disclose, teach, or suggest gas-containing microparticles.

Therefore, as Berg fails to disclose gas-containing microparticles, Applicants respectfully submit that the present invention is patentably distinct therefrom. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1-12 and 18-22 stand rejected under 35 U.S.C. §102(b) as being anticipated by Lohrmann (United States Patent No. 5,716,597).

US 5,716,597 (hereinafter, the '597 patent) relates to an oil-in-water emulsion comprising a water-insoluble gas-forming chemical and a stabilizer. Applicants submit that the oil-in-water dispersions of the '597 patent are simply such dispersions, i.e. no further materials which could provide nucleation sites, in particular gas-containing nucleation sites, are added. Hence, the dispersions of the '597 patent do not contain or comprise heterogeneous nucleation sites. Moreover, the '597 patent fails to suggest dispersions having heterogeneous nucleation sites.

Therefore, as the '597 patent fails to disclose each and every element of the claimed invention, Applicants respectfully submit that the present invention is patentably distinct thereover. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim rejections – 35 USC § 103:

Claims 1-22 stand rejected under 35 U.S.C. §103(a) as being anticipated by any one of Apfel, Berg, or Lohrmann in view of Unger (WO 98/10799). This rejection is respectfully traversed.

The Examiner contends that the present invention is unpatentable over any of Apfel ('097), or Berg ('301), or Lohrmann ('597) in view of Unger (WO 98/10799). The Examiner notes that Apfel, Berg, and Lohrmann fail to disclose compositions including a vasodilator and Berg and Lohrmann fail to disclose the addition of a drug. The Examiner cites Unger for the use of vasodilators in ultrasound imaging and for the addition of a

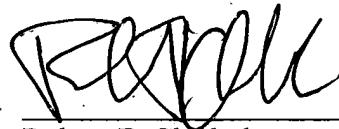
drug. Unger is therefore only cited for teachings which are the basis of dependent claims 13-17.

Applicants respectfully submit that Unger fails to correct the deficiencies of Apfel, Berg, and Lohrmann presented hereinabove, nor even does the Examiner conclude that it does so. Furthermore, in contravention of the Examiner's assertion, the application of Unger to any of the cited references fails to disclose, teach, or suggest claims 13-17. As claims 13-17 are dependent claims, the allowability of the base claims over Apfel, Berg, and Lohrmann render the dependent claims allowable as well. In view of Unger failing to correct the noted deficiencies of the cited references, Applicants respectfully submit that claims 1-20 are patentably distinct thereover. Reconsideration and withdrawal of the rejection are respectfully submitted.

In view of the remarks set forth hereinabove, Applicants respectfully submit that the present application, including claims 1-20, is in condition for allowance. Favorable action thereon is respectfully requested.

Any questions with respect to the foregoing may be directed to Applicants' undersigned counsel at the telephone number below.

Respectfully submitted,



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case of incompressible phases. This chapter is divided into four sections, dealing with (i) the formation of bubbles, (ii) the growth of bubbles, (iii) the detachment of bubbles, and (iv) the role of surfactants in bubble formation and stability.

6.2 Formation of bubbles

We can broadly separate bubble formation into two categories: those cases where the free energy of the system is reduced by the appearance of bubbles, thus being spontaneous in the thermodynamic sense; and those where bubble formation is accompanied by a corresponding increase in the free energy.

6.2.1 Spontaneous bubble formation

Bubbles may be formed spontaneously in several ways, but note that bubbles can form spontaneously in a single-component system only by cavitation or boiling (ebullition), whereas in a two (or greater) component system supersaturation of a second component may arise, and hence under appropriate conditions bubbles may be formed as a result of the presence of a greater than equilibrium concentration of a dissolved gas, as well as by the two previously mentioned mechanisms. Note, however, that a dissolved gas may have an effect upon the boiling of the major component, even if it is itself insufficiently supersaturated to produce bubbles, as noted by Mori *et al.* (1976).

Conceptually, boiling in a single-component system, and the formation of gas bubbles of a second component, are similar. Where the second component does have an important influence (see Section 6.4 for the effect on surface tension and contact angle) this will be discussed in the context of specific alterations to an otherwise unified approach.

Bubbles may arise spontaneously from six quite separate and essentially independent sources, and in each case after their formation, growth to a macroscopic size may take place:

- (a) homogeneous nucleation
- (b) heterogeneous nucleation
- (c) cavitation
- (d) electrolysis
- (e) Harvey nuclei
- (f) pre-existing and colloidally stable free bubbles.

Controlled Particle. Dreyfus and Duson (1954) have shown that the nucleation rate in a binary system of $\text{C}_2\text{H}_5\text{OH}$ and H_2O is increased by the presence of a solid particle of CaCO_3 of size 10^{-4} to 10^{-5} cm. The rate of nucleation is proportional to the square of the particle size, and the rate of nucleation is thus increased. They are more important for that reason. In fact, in practical situations such as freezing gas phases, it may be possible to avoid and for this reason nucleation will not be significant.

Homogeneous nucleation; single-component system.

When bubbles are formed in the bulk of the liquid, well away from any surfaces or the walls of the container, dust particles or other foreign bodies, or for example, the walls of the container, then the nucleation is said to be 'homogeneous'. The free liquid surface, then the nucleation is the excess of chemical potential of the liquid phase as compared with that of the vapour and, for the purposes of the present chapter, this drive may arise in two chief ways.

Alteration of temperature

In a single-component system, raising the temperature of the system at a constant pressure (usually close to but not exactly equal to atmospheric) sufficiently above the appropriately pressure-corrected boiling point will result in the formation of initially critical-sized bubbles, which will then rapidly grow. The pressure correction and the inequality to atmospheric pressure arise from the fact that there is a hydrostatic head to be considered. Usually, this correction is small, but in dense liquids, or at great depths, these could be significant. In this context, it is worth noting that, given a spatially uniform temperature for the liquid (in practice, convection will render the liquid thermally inhomogeneous), boiling should start near the top of the containing vessel where the hydrostatic pressure is least. The liquid surface itself may be the preferred site for nucleation, where the role of inhomogeneities will be important. Chief amongst these is likely to be the presence at the interface of surface active species, which might either promote or antagonize nucleation (see Section 6.5). A purist might further argue that such nucleation at the free liquid surface is not actually homogeneous in any case, and should for this reason be considered in the section on heterogeneous nucleation (see below).

Alteration of pressure
 The vapour may be stabilized with respect to the liquid by a reduction of pressure. It is of course a commonplace that reducing the pressure above a liquid will cause a reduction in the boiling point. Similarly, reduction of the hydrostatic pressure in a liquid can cause cavitation, and this problem has a mature and extensive engineering literature (see e.g. Knapp *et al.*, 1970). For example, the power that can be transmitted by a screw (propeller) to the surrounding water before the reduction in hydrostatic pressure over the trailing edges causes cavitation (and collateral damage to the material of the screw) limits the efficiency of screw-driven vessels. Studies of the (negative) pressure required to cause breaking of a thread of liquid contained in a capillary tube have a venerable history, and have been used extensively to test theories of cavity nucleation. Most experiments have actually revealed that the nucleation of cavities is not aqueous, but takes place preferentially at surface imperfections, probably

related to Harvey nuclei (see Section 6.2.3). Note that evacuating the head space of a beaker liquid can only impose a negative pressure or tension of (at most) 1 atmosphere, whereas mechanically imposed tensions larger than this can be achieved by other procedures, as discussed in Section 6.2.3.

The thermodynamic kinetic treatment of homogeneous, single-component systems nucleation applies equally to the two above chief ways of supersaturating the system, and also with minor modification, to the formation of bubbles in two (or more) component systems.

The theory of both homogeneous and heterogeneous nucleation has been covered extensively in the literature. Particularly comprehensive reviews have been given by Hirth and Pound (1963) and by Zettlemoyer (1969), while an earlier work by Dunning (1955) is still unsurpassed for clarity. More recently, Kashtiev has published several excellent articles covering both atomistic and so-called 'classical theories' (Kashtiev and Exterova, 1980; Kashtiev, 1982, 1984, 1985; Exterova *et al.*, 1983; Gussov *et al.*, 1985; Telyukov and Kashtiev, 1986). It is noteworthy that bubble nucleation does not have an extensive review literature, and only rates a mention in the review of Hirth and Pound. In view of the large number of general nucleation reviews, only a superficial treatment is given here, for understanding the later complications.

given here, sufficient for understanding ...

In general, homogeneous nucleation occurs at higher supersaturations than for the heterogeneous case, and the theoretical prediction is that under conditions of low supersaturations, homogeneous nucleation is unlikely. The other way of expressing this is that the rate of heteronucleation for a given supersaturation is likely to be much greater than the corresponding homonucleation rate. Such a statement carries a risk of misinterpretation, however, since the heteronucleation rate will always be limited at sufficiently high rates, by the number of hetero-sites. In the case of homogeneous nucleation, the ultimate rate would not be limited in this way, though it would of course be limited by the diffusion of monomer units to the growing nucleus.

To emphasize this, consideration of the CO_2 -water system shows that the conditions for homogeneous nucleation of CO_2 bubbles requires a supersaturation in excess of about 1000: this should be compared with a typical supersaturation of about 4 for commercially carbonated drinks, for example. The experimental finding is, of course, that many bubbles are indeed formed in such systems. Conditions for homogeneous nucleation are fairly infrequently met, and thus despite its theoretical importance, this type of nucleation is often not as practically significant as the heterogeneous case.

Before discussing the kinetic expressions for J , the rate of nucleation under various conditions, we introduce the concept of a 'critical' size. It is helpful first to examine the concept of critical size in the case of a liquid drop formed from a supersaturated vapour. A supersaturated vapour is thermodynamically less stable (and therefore has a higher chemical potential) than the liquid. The free energy of formation of a drop of the (new) liquid phase of radius r is composed of two terms – the 'surface' term and the 'bulk' term. The surface term expresses the fact that energy must be expended to form the drop/vapour interface of

$$\Delta G_{\text{surface}} = 4\pi r^2$$

The bulk term is due to the gain in free energy as a result of the greater stability of the liquid phase, ΔG , per unit volume of new phase.

$$\Delta G_{\text{bulk}} = 4\pi r^3 \Delta G/3$$

Overall, the free energy change is given by

$$\Delta G_{\text{total}} = 4\pi r^3 \gamma - 4\pi r^2 \Delta G/3 \quad (6.3)$$

Now, the Kelvin equation (eqn (6.4)) relates the curvature of the interface ($1/r$) to the ratio of the vapour pressure P of a drop of radius r to that over a flat surface P_0 , where $\alpha = P/P_0$:

$$2\gamma/r = kT \ln \alpha \quad (6.4)$$

and ΔG , can be expressed in terms of α , since for a molecular volume of 0

$$\Delta G_V = kT \ln \alpha/0 \quad (6.5)$$

As can be seen from Figure (6.1), ΔG_{total} passes through a maximum at a size r^* , given by differentiating ΔG_{total} with respect to the radius, and setting the resulting expression equal to zero. This gives the maximum free energy barrier, ΔG^* , which has to be surmounted in the nucleation process. The size of the droplet r^* corresponding to this maximum in the free energy is called the critical drop size. If such a drop loses one molecule (monomer unit), it will have an increasing propensity to evaporate, since its curvature is now greater than $1/r^*$, and from eqn (6.4) this results in an increased vapour pressure; finally, the droplet will thus return to individual molecules. If, on the other hand, it gains a molecule, it becomes essentially free growing, since its curvature is now decreased, and its vapour pressure correspondingly reduced below that of the ambient supersaturated vapour. The equilibrium at the size r^* is thus unstable, and the formation of critical-sized droplets is the kinetic bottleneck to the appearance of the new liquid phase from the supersaturated vapour.

A very similar argument leads to the definition of the critical bubble size, and a full analysis of the problem is given by Blander and Katz (1975). In terms of P and P^* , the pressures in the liquid and the vapour pressure of the liquid (at the ambient pressure P), respectively, and the surface tension γ :

$$r^* = 2\gamma/(P^* - P) \quad (6.6)$$

In terms of measurable quantities, since $\alpha = P^*/P$, and $\sigma = \alpha - 1$, this gives approximately:

$$r^* = 2\gamma/\sigma P \quad (6.7)$$

At this size, the bubble is in mechanical equilibrium with the liquid, and the chemical potential of the vapour in the bubble is equal to that of its surrounding liquid.

In order to predict the rate of nucleation, we need to calculate (i) the number of critical-sized bubbles formed per unit time, and (ii) the rate at which they acquire one extra molecule, and thus become free growing. We start by considering the case of boiling (ebullition) in a single-component system. The most important parameter is (as before) the saturation ratio α , which for boiling

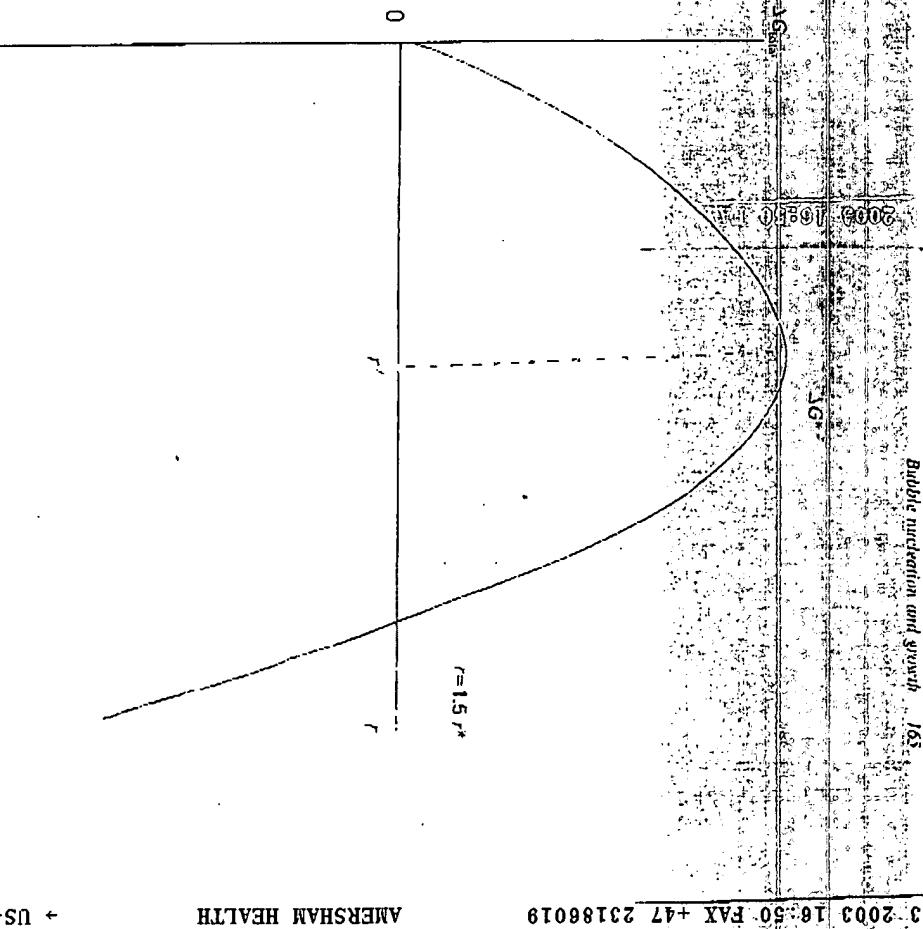


Figure 6.1 The overall free energy (ΔG_{total}) for the formation of a cluster passes through a maximum with increasing size of the cluster. The size corresponding to this maximum free energy requirement occurs at the radius r^* , and since the free energy decreases in both directions away from this maximum, the drop will either grow or evaporate; the equilibrium is unstable. The quantity ΔG^* (corresponding to r^*) is thus the maximum free energy barrier in the nucleation process, and constitutes the kinetic 'bottleneck' to the formation of the new phase. Once such a critical nucleus has been formed by fluctuations (whose probability decreases in proportion to $\exp(-\Delta G^*/kT)$), the stability of the mother phase (supersaturated vapour in this case) is threatened. The point at which the curve crosses the x-axis, which occurs at $r = 1.5r^*$, corresponds to the cluster size at which the surface and bulk terms exactly balance – it has no great significance insofar as nucleation theory is concerned.

is a measure of the degree to which the liquid is supersaturated above its normal boiling point under the prevailing conditions of pressure—both applied (often atmospheric) and hydrostatic.

In this equation, J_0 (i.e. the number of bubbles formed per second per unit area) is given by the equation (6.8) for the concentration of dissolved gas, and C is given by (6.8)

$$C = \exp [-16\pi\gamma^3/3kT(\sigma P)^2] \quad (6.8)$$

in this equation, ρ^* is the partial pressure of the vapour in the critical bubble, and is equal to $P + 2\gamma/b$, where P is the applied hydrostatic head. C is a quantity which varies relatively slowly with σ , the supersaturation, defined as above, $\sigma = \alpha - 1$, and T . The value of C can usually be considered to be approximately constant for small ranges of supersaturation. In those instances where such approximations are not valid, a fuller account must be taken of the parameters going to make up C . According to Döring (1937, 1938), C is given by

$$C = [6\gamma/\pi m(3 - b)]^{1/2} \cdot \exp (-\Delta H_{\text{vap}}/kT)^{1/2} \quad (6.9)$$

where γ is the interfacial tension between the liquid and its vapour at the appropriate temperature, m is the molecular mass, ΔH_{vap} is the enthalpy of vaporization per molecule, and n_h is the number of molecules per unit volume (1 cm^3 in the present context). The quantity $b = (\rho^* - P)/\rho^*$ introduces a problem, since for $b > 3$ this leads to a negative square-root term. Döring thus restricted his equation to cases where $b < 3$. This problem was surmounted by Hirth and Pound (1963) who give as an alternative to eqn (6.9) for C :

$$C = \Delta G^*/(3\pi kT\gamma^2)^{1/2} \cdot \rho^*/(2\pi m kT)^{1/2} \cdot 4\pi r^{*2} \cdot n_0 \quad (6.10)$$

This can also be expressed in other terms which emphasize the similarities with eqn (6.9)

$$C = \Delta G^*/(3\pi kT\gamma^2)^{1/2} \cdot n_g v \exp (-\Delta H_{\text{vap}}/kT) \cdot 4\pi r^{*2} \cdot n_0 \quad (6.11)$$

where n_g is the number of molecules per square centimetre in the liquid surface, and v is the vibrational frequency of the liquid molecules.

In order to compare experimental results with eqn (6.8), together with expressions (6.9), (6.10) or (6.11) for the pre-exponential, a means of evaluating ρ^* is needed. Hirth and Pound (1963) showed that the transcendental eqn (6.12) provides the required expression

$$kT \ln (p/p^*) = \Omega(p^* - P) \quad (6.12)$$

Homogeneous nucleation, two-component system

Let us now briefly consider the case of a two-component system, where the second component is a dissolved gas. With small modification, the equations developed above are used again. There are two main modifications required to the theory, these being that the effective pressure in the critical bubble nucleus is increased by the presence of the dissolved gas, and the modification of the surface tension by the dissolved gas.

Firstly, the pressure inside the bubble p^* is now composed of the sum of the

(partial) vapour pressure of the liquid P_1 , together with the partial pressure of the dissolved gas, P_2 .

The same authors showed that $P_1 = \varphi P_{\text{vap}}$ where φ is given by

$$\varphi = \exp \{ \Omega(P - P_{\text{vap}})/k(T - c_2/c_1) \} \quad (6.14)$$

here Ω is the molecular volume of the solvent and c_1 is the solvent concentration in moles per unit volume (ca. 55.5 M for water). With these modifications, the nucleation equation reads

$$J = C' \exp [-16\pi\gamma^3/3kT(Pc_2/c_{2e} + \varphi P_{\text{vap}} - P)^2] \quad (6.15)$$

where use has been made of eqns (6.14) and (6.15). Now, C' is not strictly a constant (as before), but includes N , the number of molecules per unit volume of solvent, a factor B (= 1 in the present discussion), the surface tension γ , and the molecular mass of the gas species m . The interested reader is referred to Ward *et al.* (1970, 1986) for details. Lubetkin and Blackwell (1988) showed that at low supersaturations, where $\varphi P_{\text{vap}} \ll P c_2/c_{2e}$, then the bracketed denominator in eqn (6.15) simplifies to give

$$J = C' \exp [-16\pi\gamma^3/3kT(\sigma P)^2] \quad (6.17)$$

where σ is the saturation ratio, $\sigma = c_2/c_{2e}$ (see eqns (6.7) and (6.16)), minus one; thus $\sigma = \alpha - 1$. Equation (6.17) is now in a form to be directly compared with experimental data.

Secondly, the adsorption of the dissolved second component will in general alter the interfacial tension. Since this quantity, γ , appears to the third power in the exponential, it will exercise a considerable influence on the rate of nucleation. This question is addressed in detail in Section 6.4.

Heterogeneous nucleation, single-component system

Bubbles formed at a surface (e.g. the walls of the container, specks of dust or other inhomogeneities), rather than in the bulk of the solution, are said to be nucleated 'heterogeneously'. Usually, heterogeneous nucleation of bubbles is easier (i.e. occurs at lower values of σ) than for the homogeneous case. The degree to which it is easier varies according to two main parameters: (i) the contact angle θ of the gas/solution/solid interface; and (ii) the geometry of the nucleation site.

The contact angle θ As the contact angle increases away from zero (where nucleation is exactly as difficult as for the homogeneous case), it becomes easier for bubbles to be

formed. Mathematically, this increased ease of formation is expressed by the introduction of a factor $f(\theta)$ in the exponential term, $f(\theta) \exp[-E/(kT)]$, and the equation

$$J = C \exp[-E/(kT)] f(\theta)^{1/4} \quad (6.18)$$

now includes a further two terms, which depend upon the contact angle. The first is simply, $f(0) = 1$, and the second, $f(180^\circ) = 1/2(1 + \cos(\theta))$. As before, we note that changes in the pre-exponential are usually negligible in their effect on J , when treating the pre-exponential as a constant.

Thus, $f(\theta)$ is given by

$$f(\theta) = [2 + 3 \cos(\theta) - \cos^3(\theta)]/4 \quad (6.19)$$

This function changes from 1 when $\theta = 0^\circ$ (i.e. 'perfect wetting') to 0 when $\theta = 180^\circ$ and, correspondingly, the free energy barrier to the formation of bubbles changes from a size as large as that for the homogeneous case when $\theta = 0^\circ$ to zero when $\theta = 180^\circ$.

Conceptually, the easiest way to understand this reduction in free energy needed for nucleation is to note that, as the contact angle increases away from zero, so the critical bubble will adopt the shape of a spherical cap, whose volume is governed by the contact angle, as shown in Figure (6.2).

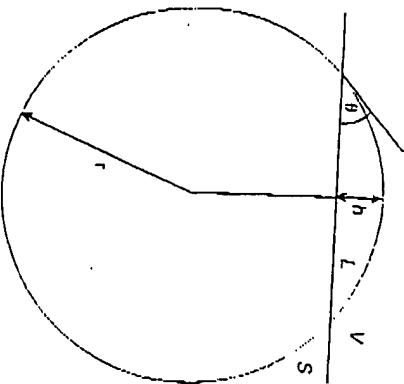


Figure 6.2 The spherical cap model of a nucleus of a partially wetting liquid forming on a solid surface. The maximum height of the cap h is a function of the sphere radius r and the contact angle θ . Eliminating h from the expression for the volume of the cap gives the function $f(\theta)V = [2 - 3 \cos(\theta) + \cos^3(\theta)]^{1/4}$, where V is the volume of the whole sphere, of radius r . The function $f(\theta)$ goes from 1 for $\theta = 180^\circ$ (i.e. non-wetting), to zero for $\theta = 0^\circ$ (i.e. perfect wetting). Note that this is the opposite of the case for bubbles, where the function $f(\theta)$ goes from 0 to $\theta = 180^\circ$ (i.e. non-wetting), to 1 for $\theta = 0^\circ$ (i.e. perfect wetting), as expressed by eqn (6.19).

The geometry of the nucleation site
The problem of nucleation in a two-component system has not yet been fully investigated, but no analysis is available for heterogeneous nucleation, two-component system by Cole (1974).

Heterogeneous nucleation, two-component system

Equation (6.17) can be modified to take account of variations in the contact angle θ and in the geometry of the nucleation site for the case of heterogeneous nucleation in two-component systems. Essentially, it is found that nucleation becomes considerably easier in certain cases, and in particular for conical pits. A conical pit of half-angle β , introduces a factor in the exponential term (and also into the pre-exponential term, which we are ignoring in the present analysis) which reduces the barrier to nucleation. If we take the effect of the contact angle and the conical pit together, the factor can be called $f(\theta, \beta)$, and is defined as

$$f(\theta, \beta) = [2 - 2 \sin(\theta - \beta) + \cos(\theta) \cos^2(\theta - \beta) \sin(\beta)]^{1/4} \quad (6.20)$$

and the modified nucleation equation becomes

$$J = C''' \exp[-16\pi\gamma^3 f(\theta, \beta) kT(\sigma P)^2] \quad (6.21)$$

With these modifications, and for some values of γ , θ , β and σ , eqn (6.21) predicts reasonable rates of formation of bubbles under conditions of supersaturation easily attainable in practice. As a concrete example, for the CO_2 -water system, supersaturations of around 4 are sufficient to cause nucleation in cavities of half-angle of about 5° , with contact angles of about 90° (Wilt, 1986). The factor $f(\theta, \beta)$ becomes negative when $\theta - \beta > 90^\circ$, and the treatment breaks down (Carr, 1993). The factor $f(\theta, \beta)$ used by Wilt is chosen to give a very small numerical value (ca. 10^{-5}), and it is chiefly this which results in predictions of reasonable rates of nucleation at low supersaturations. Small changes in either θ or β result in such large (negative) values of the exponential term in eqn (6.21) that it becomes impossible to evaluate the full expression for J . The whole basis of the analysis above has been criticized (Lubelkin, 1989a, b), and this is referred to below (Section 6.4).

Single-component nucleation experiments – boiling

This field is really too large for a satisfactory treatment here, and the interested reader is referred to Cole's (1974) review. Briefly, early experiments (see e.g. Wismer, 1922) attempting to measure superheat limits on bulk samples of liquids gave sometimes confusing and irreproducible results. The most likely explanation for such apparent experimental failures is that Harvey nuclei (and more generally heterogeneous nucleation sites of unknown detailed geometry and contact angle) were promoting nucleation or bubble formation. These early experiments all share the feature that the superheat limits are not as large as theoretically expected. Deliberately roughened surfaces were employed by Cory and Foust (1955), while Clark *et al.* (1959) used macroscopically polished

surfaces for their high speed photographic investigations, and identified individual nucleation sites. A point of view of nucleation kinetics on the basis of promising results of the theory of the kinetics of condensation processes in the droplets of condensate droplets is presented. Such a procedure may be used in studies of crystallization processes. Sander and Blundell (1973), Blundell (1975a, b), Anton (1976) those using this approach were Treloar (1957), Awasthina and Fukada (1958), Skripov and Sintsyn (1964), Treloar (1957), Awasthina and Fukada (1958), Skripov and Sintsyn (1964, 1968) (see also Skripov and Ermakov, 1965; Sintsyn and Skripov, 1968; Blundell and Sander, 1973).

(Meyer, 1911; see also Kenrick *et al.*, 1924). The direct application of negative pressures by bellows (Vincent, 1941, 1943) and centrifugal methods have been used more recently (Bagnall, 1950, 1951; Bagnall and Garside, 1953, 1955). As noted earlier, experiments generally were conducted with extensions much lower than those calculated from the theory. This is illustrated by Table 5, to which shows the calculated and experimental values of various quantities. The discrepancy between prediction and experiment leads to the conclusion that cavitation (in common with many other nucleation phenomena) is normally heterogeneous, unless special precautions are taken.

Two-component nucleation experiments Reports of experiments on bubble nucleation

Reports of experiments on bubble nucleation in supersaturated gas solutions (other than electrochemically evolved gasses) are rare, although there is a substantial qualitative and semiquantitative literature on the gas content of carbonated drinks (see, e.g. Findlay and King, 1913). More recently, Lubeikin and Blackwell (1988), and Lubeikin (1989a, b) have reported measurements on the rate of nucleation of bubbles of CO_2 from supersaturated water solutions, and attempted to compare the results with the classical heterogeneous nucleation theory of Wilf (1986) with rather variable results. The interpretation of the data shows that the nature of the hetero surface, and in particular the degree to which it is hydrophilic or hydrophobic, has important consequences. This is discussed more fully in Section 6.4.

Cavitation is the process of bubble formation by reduction in pressure. The reduction may be effected by mechanical means, placing the liquid under tension, or by acoustic means, where rarefaction waves similarly introduce negative pressures. It is of interest to note that the elementary step in the growth to supercritical size of the cavity nucleus is not (as might be supposed) the transfer

The question of the further growth of the bubbles once from liquid to growing cavity (Smith and Fowles, 1955).

The question of the further growth of the bubbles once formed appears not to have been studied, and will not be further addressed here, except to note that if the bubble has been produced by a transitory change in pressure (as might be expected in the case of cavitation produced by acoustic means) there is no obvious drive for further growth - indeed, it is often the extremely rapid collapse of the cavities which liberates enough mechanical energy to cause the damage found on ships' screws. Clearly, in a solution that is supersaturated, but insufficiently so to give spontaneous nucleation, cavitation could potentially provide supercritical nuclei, and the further growth of these nuclei would then be assured, assuming that transport of the growth units was adequately fast to outpace incipient bubble collapse.

Cavitation experiments have been conducted using a variety of techniques. The earliest attempts were made by completely filling glass tubes with liquid, sealing and then cooling them; from the known thermal expansivities of the glass and the liquid, the observed rupture could be related to a calculated tensile

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Liquid	Theoretical fracture pressure (atmos)	Observed fracture pressure (atmos)
Water	-1380	-270
Chloroform	-318	-290
Benzene	-152	-150
Acetic acid	-325	-288
Aniline	-625	-280
Carbon tetrachloride	-315	-275
Mercury	-23100	-425

"Courtesy of Kirtch and Pound (1963)"

Electrolytic and chemical bubble generation

Electrolytic bubble generation
 This is a wide topic and really deserves a review in itself, and many have been published; for a recent example, see Sides (1986). However, in general terms, electrolytic bubble generation is not markedly different from heteronucleation and growth on surfaces other than those of electrodes. It should be remarked, however, that bubbles will in general be charged, and the electrode surface itself will carry a charge, the sign and magnitude of which will vary as the electrochemical conditions are altered. This introduces a variable interaction between the hetero surface and the growing nucleus/bubble not met in other cases of heterogeneous nucleation.

This specific interaction will alter both the thermodynamics (through changes in the electrochemical potentials of the various species and phases) and the kinetics (by altering diffusion rates, for example). Furthermore, it is to be expected that the size of the bubbles upon detachment from the electrode will be strongly influenced by subtle changes in composition of the electrode surface, and by the electrostatic interaction. Some of these issues have been addressed in the literature (Brandon and Kelsall, 1985; Brandon *et. al.*, 1985).

The chief advantage of using an electrolytic method for nucleation and growth

of bubbles is that one can have full control over both their kinetics (processes) and their morphology (shape) by changing the current. In the thermodynamics of bubble formation, the gas to be trapped will be discussed in more detail below.

It should be one of the most extensively studied species—the others being hydrogen and oxygen.

White studies of the growth kinetics of electro-generated bubbles are relatively sparse. The first report of the growth kinetics of electro-generated bubbles is the work of Dinnon (see e.g. Glas and Westwater, 1964; Verhant *et al.*, 1980); few appear to have been undertaken on bubble nucleation kinetics. Indirect evidence obtained from the transient current behaviour, particularly on microelectrodes, has been used to differentiate between the importance of mass transport and diffusion, but these experiments lack in either temporal or spatial resolution. Recently, a new technique has become available which shows considerable promise in this regard. The electrochemical quartz crystal microbalance (EQCM) has great sensitivity to changes in attached mass (of the order of nanograms per square centimetre) and has been shown to be capable of detecting monomolecular layers of adsorbed species. A bubble arising at such a surface has an instantaneous effect on the apparent attached mass. The first report of this method shows that information may be obtained both on the nucleation and the subsequent growth of bubbles (Carr *et al.*, 1989), and the subsequent report of Gabrielli *et al.* (1991) confirmed the promise of this novel method.

Chemical bubble generation

The supersaturated gas/liquid solution can of course be produced by a chemical reaction which does not involve the passage of an electric current. Thermal decomposition reactions producing gases are the most obvious type to exploit, and current practice uses carbonates, nitrates, hydrogen peroxide, and diazo derivatives. Thermal decomposition can be replaced by acid-base reaction, or other chemically induced gas releasing processes. In urethane foam production, the carbon dioxide gas released in the reaction of the isocyanates may be used to produce the foam. Careful control of the initial particle size of the chosen reactant(s) provides the possibility of complete control of the final bubble size, but the thermal instability of many of the obvious candidate reactants may inhibit mulling to the appropriate size.

Harvey nuclei

The formation of macroscopic bubbles may take place without the need for a nucleation step, if there are pre-existing sources of bubbles. Here and in the subsequent sections, we consider three such sources: Harvey nuclei and pre-existing bubbles whose size is sufficiently small to prevent creaming under gravity, and entrained or sparged bubbles. The distinction between these is not simply a matter of where the pre-existing bubble is located (although for Harvey nuclei this must be at a solid-liquid interface, by definition (Harvey *et al.*, 1944a, b, 1945, 1947; see also Bankoff, 1958), but includes possible differences

in size of the bubble source. In the case of Harvey nuclei, the source is any gas-filled (usually) re-entrant cavity of such geometry and size that the entrapped gas

is supersaturated to displacement of the surrounding liquid phase. The size requirements are not as strict as the dissolved gas requirements that the trapped gas be the same as the dissolved gas or

chemical composition.

For the present, suffice it to say that bubble suspensions are frequently less concentrated than other conventional colloidal systems, so that Brownian collision, and hence coalescence, is less important. For the case of supersaturated gas solutions at least, there is no problem of dissolution for supercritical-sized bubbles. Furthermore, surfactants may play an even more important role in stabilising bubbles than in other colloidal systems, and this aspect is dealt with more fully in Section 6.5.

The thermodynamic and to a lesser degree the hydrodynamic requirements for the stability of Harvey nuclei have been studied by Cole (1974), while the behaviour of sites of known geometry during boiling of water were tested experimentally by Griffith and Wallis (1960). In the case of bubble formation from a supersaturated gas solution, similarly well-defined sites were examined by Lubetkin (1989b).

Pre-existing bubbles

Most liquids which have been subject to shaking or stirring in a container will contain bubbles. Naturally, because of the generally large density difference between liquids and vapours or gases, creaming will take place on a time-scale determined by bubble diameter. For a given liquid/vapour combination, the importance of creaming will be regulated by the Peclet number, which is defined as the ratio of the gravitational force to the Brownian force on the bubble:

$$P_e = \Delta \rho g r / kT \quad (6.22)$$

where $\Delta \rho$ is the density difference between liquid and bubble, r is the bubble volume, r its radius, k is the Boltzmann constant, and T the absolute temperature. Creaming will only be important where $P_e \gg 1$, which for water at room temperature will be satisfied for bubbles of rather more than 1 μm in diameter. Obviously, bubbles much smaller than this size will not cream on reasonably short time-scales, and as they become smaller still, they will effectively not cream at all. Such behaviour is well known for colloidal dispersions of solids and liquids, and the potential long-term (kinetic) stability of such suspensions hardly needs re-emphasis here. The issue is not settled by such an analysis, however. Stability against creaming or sedimentation is no guarantee of stability in other respects, and so it is here: bubbles are as subject to dissolution and coalescence as are liquid droplets or solid particles. These issues are addressed in Section 6.4. For the present, suffice it to say that bubble suspensions are frequently less concentrated than other conventional colloidal systems, so that Brownian collision, and hence coalescence, is less important. For the case of supersaturated gas solutions at least, there is no problem of dissolution for supercritical-sized bubbles. Furthermore, surfactants may play an even more important role in stabilising bubbles than in other colloidal systems, and this aspect is dealt with more fully in Section 6.5.

In the case of aqueous media, it is known that bubbles may be very persistent.

The original work of Hawley *et al.* (1944, b, 1945, 1947) and Bunkoff (1938) demonstrated that bubbles of these sizes could not be broken by a review of the literature, it appears that Renshaw and Darragh (1939) has received the first demonstration of the stability of bubbles of this size. In this paper, the authors give data for such simple bubbles, but for which the ambient water contains at least one type of inhibitor. The authors also discuss what the response of their bubbles would be to the addition of a second inhibitor. The results of this work are summarized in Table I. It is highly interesting to note that the bubbles are stable, that is, they do not burst, when the inhibitor concentration is high enough. The bubbles will contain a large number of bubbles, and statistically, a proportion of these will satisfy the Peclat criterion, and be kinetically stable over long periods of time. The bubbles considered by D. A. Igo are generally much larger than thus non-creaming size (say between about 30-100 μ m in diameter), and his chief interest

A sudden change in conditions in such a stable bubble-containing system (reduction of pressure, increase in temperature etc.) would then give rise to a surge of bubbles, as the pre-existing, submicroscopic bubbles rapidly grew to a visible (or detectable) size. The appearance would be of a rapid burst of nucleation, but such an impression might be false: no nucleation would be needed, and none might have taken place; this could only be decided on the basis of whether the imposed change was sufficient to cause nucleation on its own account, and by whether the rate of bubble appearance dropped with time more rapidly than the rate of relief of supersaturation apparently warranted.

From a practical standpoint, the interesting question is how long might such pre-existing bubbles last? Unfortunately, there seems to be no clear answer to this question at present. By analogy with colloidal suspensions of solids or liquids, however, we may speculate that the life-times may be very long, indeed. Faraday's original gold sols are still stable at the Royal Institution in London, nearly 150 years after their preparation. It is relatively easy to give an answer to the related question of how to get rid of the bubbles: the application of a sufficiently great pressure will collapse all bubbles in the system, the magnitude of the pressure required will of course depend on the size of the bubble to be removed. Rather more discouragingly, these pressures are often very large, and in excess of 1000 atmos. Worse still, there is always the prospect that upon reduction of the applied pressure, that the released gas will again nucleate to form a fresh crop of microbubbles.

6.2.2 Non-spontaneous bubble formation

The term 'sparging' is intended to cover the insertion of gas bubbles directly into a liquid by pumping gas (usually through a frit, filter or bubble column) into the bulk liquid. In principle, this should be the most controllable and reliable method of producing monosized bubbles, and furthermore the theory is reasonably well understood. The thermodynamic factors ruling bubble production at an orifice are the subject of an extensive literature. We note that the mathematics of the size and shape of a bubble forming at an orifice are identical (with an appropriate sign)

$$2\pi r \sin(\phi) = \Delta p g + \pi r^2 \Delta p \quad (6.23)$$

where x is the horizontal distance to the bubble axis at an angle ϕ to that axis, V is the bubble volume, $\Delta\rho$ is the density difference between gas and liquid, and g is the acceleration due to gravity. The pressure drop Δp across the interface at any point is given by

Making use of the Laplace equation relating the principal radii of curvature R_1 and R_2 to the components of the metric tensor, we have

and R_2 to the difference in pressure Δp across the curved interface and to the interfacial tension γ :

$$\Delta p = \gamma(1/R_1 + 1/R_2) \quad (6.25)$$

This equation can be written in dimensionless form using a parameter β , related to the bubble shape, and given by

$$\beta = \Delta \rho g b^2 \gamma \quad (6.27)$$

b is the radius of curvature at the apex of the ditonne. Combining these parameters into a single equation gives

$$[1/(R/b)] + [\sin(\phi)/(x/b)] = \beta(z/b) + 2 \quad (6.28)$$

This is the form of equation solved numerically (by hand) by Bushforth and Adams (1883). More conveniently, the required quantities can be expressed in terms of two characteristic diameters of the bubble d_e and d_s , where d_e is the diameter at the equator of the bubble and d_s is the diameter at a distance d_s from the apex. The ratio d_s/d_e is often called S , which is experimentally determined and defining a new quantity H given by

$$H = \beta(d/b)^2 \quad (6.25)$$

it follows that

$$\gamma = g \Delta \rho d_e^2 H \quad (6.3)$$

Equation (6.30) is exact, and tabulated values of S as a function of $1/H$ are readily available. Knowing (experimentally) the value of S , the tables give the appropriate value of H , and thus from eqn (6.30) γ can be determined. This

perhaps the most convenient method for relating bubble size and shape to the physical conditions in the bubble chamber is to measure the dependence of the measured bubble volume (often referred to as *mean bubble volume*) on the pressure (or density) of the surrounding gas. This is a valuable, though often rather difficult, procedure for determining absolute quantities, such as the total number of bubbles, bubbles of a given size, and so on.

empirical correlations (Boucher and Evans, 1975; Boucher and Kent, 1978; Boucher, 1980). In most cases of sparging, equilibrium calculations are inadequate to predict the disengagement volume. Usually, the dynamics of the fluid-fluid interface have to be accounted for since rapid bubble formation is usual in sparging. This is a more difficult problem, and while empirical correlations are available (Perry *et al.*, 1984), little is known theoretically. Three regimes can be distinguished: the single bubble regime, the intermediate regime, and the jet regime. The single bubble regime can be reasonably satisfactorily described by the thermodynamic analyses presented above. It is simple to show that the frequency, ω , of bubble detachment for a volumetric flow rate of gas of Q , and an orifice diameter of D in a liquid/gas combination characterized by densities ρ_1 and ρ_g , respectively, is given by

In the intermediate regime, represented by Reynolds numbers of about 200-2100, the frequency of bubble detachment increases more slowly than predicted by eqn (6.3), and the bubbles themselves tend to increase in size. The jet regime is characterized by turbulence, and the appearance of 'jets' from the orifice. Despite their name, these 'jets' actually consist of many small bubbles (typically between about 200 μm and 4 mm in diameter). There is no adequate theoretical description of this regime, and even empirical correlations are not good.

Entrainment covers those situations where gas is enveloped by the liquid at the interface between the two phases, and most usually occurs where the liquid is in violent motion. Common examples are the entrainment of air into water in fountains or by wave action or other turbulent motion in oceans, rivers and lakes. Clearly, in such circumstances, the violence of the motion involved makes control of the bubble size difficult, and for this reason this method of bubble formation will not be considered in detail here. Cascade systems, where the jet of liquid is directed at an appropriate velocity into a pool of the liquid, can successfully entrain large quantities of air. An approximate expression for the volumetric ratio of gas to liquid Q_g/Q_l thus entrained is given by

where V is the jet velocity, ρ_l is the liquid density, γ is the surface tension, and L is the length of the jet.

Agitational methods are common in industrial practice, and are one of the chief means of introducing bubbles into fluid systems. Mechanical agitators may

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Attrition
 Mechanical disruption of the gas-liquid interface will usually result in the entrainment of gas. Of course, the lifetime of bubbles so formed will depend on the factors discussed below but, assuming a sufficiently long survival, these bubbles will be subject to the same mechanical/hydrodynamic processes responsible for the formation of the 'original' larger bubbles, and break up is likely to follow. These processes, which we refer to as 'attrition', are complex and there is a substantial, if mainly empirical, chemical engineering literature available (Perry *et al.*, 1984).

An elegant and revealing experiment was performed by Prins (1976), who used a rotating wire cage to measure foam volumes as a function of the tip speed of the cage, at various surfactant concentrations. In all cases, the foam volume plots showed very sharp maxima at a velocity which increased with the surfactant concentration. This velocity was identified with the critical value, beyond which the agitation caused foam breakage. It is likely that, in a general way, this sort of

behaviour would also apply to more dilute bubble suspensions, although there are good reasons for believing that dilute suspensions would not behave identically. Clearly, mechanical break up of bubbles will share common features with the similar phenomenon in emulsions, a subject which has been extensively reviewed by Tadros and Vincent (1983) and by Walstra (1983).

6.3 Growth of bubbles

Whatever the means by which a supercritical bubble is formed, it will tend to grow; growth will be fostered by the same conditions of supersaturation that gave rise to the nucleation event. Only in the case of a nucleation pulse, rapidly followed by a return to equilibrium, would further growth not take place (as noted above, such conditions may be found in acoustic cavitation). Even then if the cavity formed was sufficiently large that its Peclét number was substantially greater than unity, buoyancy would result in subsequent growth.

It is convenient to consider bubble growth at a surface and free bubble growth separately, even though they clearly have many attributes in common.

6.3.1 Bubble growth at a surface

The primary sources for information on the growth of bubbles at surfaces are from the electrochemical literature (see e.g. Westerheide and Westwater, 1961) and from the heating engineering literature. Broadly speaking, two regimes can be distinguished during the growth. Firstly, there is a short period, typically about 10 ms, where the growth is controlled by surface tension forces, inertia, viscosity and pressure, followed by growth essentially dominated by diffusion, either on